REMARKS

The present application contains claims 1-88, the status of which is as follows:

(a) Claims 57, 59-65 and 82-88 have been cancelled without prejudice.

(b) Claim 50 was previously presented.

(c) Claims 45-49, 51-56, 58 and 66-81 have been currently amended.

(d) Claims 1-44 were previously cancelled.

The Applicant thanks Examiners Fernandez and Winakur for the courtesy of an interview with the Applicant's representative, Sanford T. Colb (Reg. No. 26,856) on November 28, 2007. It was suggested by Mr. Colb that amendments be made to independent claims 45, 54, and 66 such that they recite methods and a system for determining a flow pattern of moving erythrocytes by optically imaging the moving erythrocytes within an optically accessible blood vessel of a subject. The Examiners agreed that the suggested amendments appear to overcome the prior art. The Examiners suggested that the Applicant consider US Patent 5,983,120 to Groner before filing this response.

Independent claims 45, 54, and 66 have been amended to recite methods and a system for determining a flow pattern of moving erythrocytes by optically imaging the moving erythrocytes within an optically accessible blood vessel of a subject. These amendments find support in paragraph [0022] of US Patent Application Publication 2006/0147897, which is the publication of the 10/537,116 application:

> [0022] A preferred mode of operation relies on visualizing flow in individual blood vessels, such as by the methods described in U.S. Pat. No. 6,588,901 for "Imaging and Analyzing Movement of Individual Erythrocytes in Blood Vessels" to A. Grinvald and D. Nelson, or by **tracking the movement of individual red blood cells or clusters thereof** using scanning strobed or pulsed laser light, preferably in the eye but possibly in any other place in the body.... In a vascular network embedded in living tissue, **such moving objects could preferably be the erythrocytes flowing within the blood vessels**, and a preferred way of detecting a blood vessel comprises **analyzing the spatial displacements**

of the erythrocytes in differential images for line-like patterns, preferably using standard imaging processing tools.

Additional amendments have been made to independent claims 45, 54 and 66 to enhance the clarity of these claims.

Dependent claim 56 has been amended to recite:

56. (currently amended) A method according to claim 54, and wherein said ~~change of said~~ first blood pressure corresponds to a first point in a cardiac cycle of the subject, wherein ~~to~~ said second blood pressure ~~is a result of the subject's heartbeat~~ corresponds to a second point in the cardiac cycle of the subject, and wherein steps (i) and (ii) comprise optically imaging moving erythrocytes within said at least one optically accessible blood vessel when the subject's cardiac cycle is respectively at said first and second points in the subject's cardiac cycle.

The amendments to claims 56 find support in paragraph [0071] of US Patent Application Publication 2006/0147897:

> [0071] Such perturbation also exists naturally as a result of the heartbeat of the subject, the blood pressure changing cyclically during each heartbeat. **According to a further preferred embodiment of the present invention, the imaging of the optically accessible blood vessel is synchronized to predetermined points in time of the heartbeat when the blood pressure is known to be different**, and the flow characteristics at these two points in time are compared to obtain an index for the roughness of the blood vessels.

Dependent claim 58 has been amended to recite:

58. (currently amended) A method according to claim ~~57~~ 56, ~~and wherein said synchronizing is performed by monitoring at least one~~ wherein steps (i) and (ii) comprise detecting a parameter of the subject selected from the group consisting of the ~~subject's heartbeat~~ subject's cardiac cycle and blood pressure of the subject, and ~~using said monitoring to control the timing of said optical imaging~~ optically imaging the moving erythrocytes in response to the selected parameter.

The amendments to claims 58 find support in paragraph [0032] of US Patent Application Publication 2006/0147897:

> [0032] In this above described method, the change of the first blood pressure to the second blood pressure may preferably be caused by either drugs administered to the subject or by exercise. Alterantively and preferably, the change of the first blood pressure to the second blood pressure may be a result of the subject's heartbeat. In such a case, the method also preferably comprises the additional step of synchronizing the optically imaging steps to the subject's heartbeat. **Such synchronizing is preferably performed by monitoring at least one of the subject's heartbeat cycle and blood pressure, and using the monitoring to control the timing of the optical imaging.**

Amendments have been made to dependent claims 46-49, 51-53, 55, and 67-81 to conform with the above-described amendments to the claims and/or to enhance the clarity of the dependent claims.

No new matter has been added. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. 102(e) over Flower

Claims 45-50 were rejected under 35 U.S.C. 102(b) as being anticipated by US 6,351,663 to Flower ("the Flower patent"). Flower et al. disclose a method for imaging blood flow within a blood vessel by injecting a dye into the blood vessel and taking angiographic images of the dye within the blood vessel. The Flower patent describes analyzing the angiographic images to determine whether a lesion is present in the wall of a body cavity, which the examiner asserts is the same as determining the roughness of the inner wall of a blood vessel. (The Applicant notes in this regard that examples of lesions specifically described in the Flower patent are tumors, choroidal neovascularizations, ruptured blood vessels, and abnormal vasculature.)

The method described in the Flower patent is described as enhancing the resolution of angiograms of blood vessels, by using particular compositions of dye. The images acquired using the described method are angiographic images of blood vessels. As stated in the Flower patent:

> Turning initially to the issues associated with angiogram clarity, a first aspect of the present invention provides **a method for enhancing the resolution of angiograms**. This enhancement is provided by the introduction of a plurality of relatively small, yet highly dye-concentrated, boluses of a fluorescent dye composition into an animal, and subsequently obtaining angiograms as the composition passes through the vasculature of interest. **The use of this method provides for a greater degree of fluorescence in the composition, and hence greater resolution in the associated angiogram, as compared to angiograms obtained using a composition having a conventional dye concentration.** (Column 3, line 61 to Column 4, line 5)

In some embodiments, the Flower patent described using the angiographic images to diagnose lesions:

> It should be appreciated that in connection with the various novel indications **(e.g., diagnosis and treatment of lesions, tumors and ruptured vessels, among others)** and novel carriers (e.g., liposomes and RBCs) disclosed herein, the concentration of the fluorescent dye present in the liquid composition, and the injection of relatively small boluses of the composition, is not critical. At a minimum, however, the amount of fluorescent dye used in those methods must be present in the composition at a concentration that permits the dye to fluoresce when radiation at appropriate wavelength is applied, **providing useful angiographic images**. (Paragraph 7, lines 16-26)

In the current application, the movement of individual erythrocytes, or clusters of erythrocytes within a blood vessel is analyzed to determine roughness of a wall of the blood vessel. The roughness of the wall is derived from the flow pattern of the individual erythrocytes or clusters of erythrocytes. This method differs from the method of the Flower patent, which determines properties of the blood vessel by imaging the blood vessel, by means of dye which is injected into the blood vessel. As is stated in paragraph [0016] of the current application, as published (US Patent Application Publication 2006/0147897):

> [0016] According to various preferred embodiments of the present invention there are also generally provided methods and systems for measuring, analyzing, and quantifying the status of surfaces which constrain the flow of inhomogeneous fluids. Such inhomogeneous fluids are described as those containing granularly distributed chromophores, and the measurements are performed by using the spatio-temporal patterns of flow, preferably laminar flow, in readily present or easily achievable "windows" into a larger system of "tubes". **A preferred application is the assessment of the roughness parameter of the interior surface of blood vessel walls, by characterizing the flow or movement patterns of erythrocytes in blood vessels of the living organs of a body.**

The angiographic imaging of blood vessels described in the Flower patent necessitates the presence of dye molecules within the blood vessels. In one embodiment, Flower et al. disclose a method for doping red blood cells (RBCs). The method comprises drawing blood from the subject and adding dye to the RBCs. The RBCs are then injected back into the subject and are used for diagnostic purposes.

> As mentioned above, and in a related aspect of the present invention, RBCs may be used as a carrier for the fluorescent dye. This technique is referred to herein as RBC doping. The RBC as a carrier has advantages in that it is a normal constituent of circulating blood and, despite the relative large volume (and hence large dye-carrying capacity) of each RBC, **RBCs can nevertheless readily move throughout the circulatory system--deforming to enable movement through even the small diameter capillaries**... (Column 6, lines 22-30)

It is clear from the above quotation that Flower et al. deemed advantageous the fact that RBC doping allows movement of the dye (and, therefore, imaging of blood flow) through small blood vessels.

> In a separate paragraph of the Flower patent, Flower et al. state:
>
> It should be appreciated that in connection with the various novel indications (e.g., diagnosis and treatment of lesions, tumors and ruptured

> vessels, among others) and novel carriers (e.g., liposomes and RBCs) disclosed herein, the concentration of the fluorescent dye present in the liquid composition, and the injection of relatively small boluses of the composition, is not critical. **At a minimum, however, the amount of fluorescent dye used in those methods must be present in the composition at a concentration that permits the dye to fluoresce when radiation at appropriate wavelength is applied, providing useful angiographic images.** (Column 7, lines 16-26)

Despite the desired advantage of being capable of imaging blood vessels having a small diameter, the Flower patent only discloses imaging of blood vessels using dye and not imaging of the movement of the erythrocytes themselves. Furthermore, in the above paragraph, the Flower patent teaches against imaging the blood vessel in the absence of dye.

In the present patent application, imaging erythrocytes themselves --and not the dye-- using optical imaging techniques provides a similar advantage of allowing imaging of blood flow through small blood vessels. Indeed, in paragraph [0019] of the present application, it is stated:

> The present invention is useful in imaging, analyzing or quantifying the spatio-temporal patterns of blood-flow or erythrocyte movement in retinal blood, or the spatial distribution or quantity of exogenous markers specifically binding to arteriosclerotic plaques, resolved for the different vascular compartments **e.g. in capillaries**, arterioles, venules, arteries and veins or a subset of those.

The Flower patent teaches angiographically imaging blood vessels of a subject, by means of dye which is injected into the blood vessel, the dye molecules being either uncoupled or coupled to the erythrocytes. It further describes using the angiographic images to determine the presence of lesions in the blood vessel. Claim 45 has been amended to recite "optically imaging moving erythrocytes within at least one optically accessible blood vessel of a subject," the optical imaging of the erythrocytes being without the use of dye molecules. Furthermore, claim 45 recites utilizing a flow characteristic of the erythrocytes to identify roughness on an inner wall of a blood

vessel. The Flower patent does not disclose identifying roughness (or a lesion) by determining a flow characteristic of moving erythrocytes, rather the Flower patent describes diagnosing a lesion of a blood vessel by means of an angiogram of the blood vessel. The Applicant therefore believes that the above, amended independent claim 45 does not read upon and is not obvious in light of the Flower patent. Dependent claims 46-50 are all dependent from independent claim 45, and as such they incorporate the limitations of claim 45. The Applicant therefore believes that these dependent claims are patentable over the Flower patent.

Rejections under 35 U.S.C.103

Claims 51-53, and 66-81 were rejected under 35 U.S.C 103 over US Patent 6,351,663 to Flower in view of the combination of references of:

"Retinal microvascular abnormalities and incident stroke: the atherosclerosis risk in communities study," by Wong;

"Finite element modeling of three-dimensional pulsatile flow in the abdominal aorta: Relevance to atherosclerosis," by Taylor et al. ("Taylor '98"); and

US Patent 5,279,298 to Flower.

Additionally, claims 54-55 were rejected under 35 U.S.C. 103 over US Patent 6,351,663 to Flower in view of a 2002 article entitled, "In vivo quantification of blood flow and wall shear stress in the human abdominal aorta during lower limb exercise," by Taylor et al. ("Taylor '02"). The Applicant respectfully states his assumption that the Examiner intended to write that claims 54-*58* are rejected under 35 U.S.C. 103 over US Patent 6,351,663 to Flower in view of Taylor '02. Arguments for the patentability of claims 56-58 will be made in the light of this assumption.

As stated above, the Flower patent teaches angiographically imaging blood vessels of a subject, by means of dye which is injected into the blood vessel, the dye molecules being either uncoupled or coupled to the erythrocytes. It further describes using the angiographic images to determine the presence of lesions in the blood vessel. Independent claims 45, 54 and 66 have been amended to recite optically imaging moving erythrocytes within at least one optically accessible blood vessel of a subject. As described hereinabove, the optical imaging is of the erythrocytes themselves, and

does not require the use of dye molecules. Furthermore, the independent claims recite utilizing a flow characteristic of the erythrocytes to identify roughness on an inner wall of a blood vessel. The Flower patent does not disclose identifying roughness (or a lesion) by determining a flow characteristic of moving erythrocytes, rather the Flower patent describes diagnosing a lesion of a blood vessel by means of an angiogram of the blood vessel. The Applicant therefore believes that the above, amended independent claims 45, 54 and 66 do not read upon the Flower patent. Dependent claims 51-53, 55-58, and 67-81 are all dependent from the respective independent claims, and as such they incorporate the limitations of the respective independent claims. The Applicant therefore believes that the above, dependent claims are not obvious in light of the Flower patent in combination with the above references. Additionally, the Applicant believes that Wong, the Taylor articles, the '298 Flower patent and the Groner patents described hereinbelow, separately and in combination, do not teach or make obvious the independent claims as currently amended.

US Patent 5,983,120 to Groner

The Examiners suggested that the Applicant consider US Patent 5,983,120 to Groner. In the Summary of Groner, it is stated that:

> The present invention is directed to a method and apparatus **for analysis of blood** by use of reflected spectral imaging analysis. [column 4, lines 47-49]
>
> The method of the present invention can be used **to determine various characteristics of blood.** Such characteristics can include the hemoglobin concentration per unit volume of blood, the number of white blood cells per unit volume of blood, a mean cell volume, a mean cell hemoglobin concentration, the number of platelets per unit volume of blood, and the hematocrit. [column 5, lines 36-42]

In some embodiments described by the Groner patent, the velocity of white blood cells is determined by extracting the cells from images of the blood vessel by forming a subtraction image:

> **The method of the present invention can also be used to determine the speed or velocity of white blood cells.** For example, the microvascular system beneath the mucosal membranes on the inside of the lip of a human subject can be imaged to produce the raw reflected image. To determine the speed of white blood cells, the raw reflected image can be corrected using a velocity correction. To carry out the velocity correction, the corrected reflected image is formed by taking the difference between the raw reflected image of a particular field or scene at a time t.sub.0 and the raw reflected image of the same field or scene at a time t.sub.1 where the difference in time between t.sub.0 and t.sub.1 is known. **A corrected reflected image formed by use of such a velocity correction allows moving cells to be extracted from a stationary background.**
>
> The analysis image is segmented from the corrected reflected image so that the analysis image includes large vessels. **The speed of white blood cells can be determined by tracking their movement per unit time. The speed of white blood cells can be used as an indicator of the presence of infection/inflammation** which may be more specific than the erythrocyte sedimentation rate (ESR). [column 21, first and second full paragraphs]

The Groner patent describes an experiment in which platelets and erythrocytes flowing through a flow cell, were imaged:

> A number of experiments were performed using apparatus 600 to measure various characteristics of the vascular system. For example, apparatus 600 was used to generate images of blood flowing through flow cell 630... One example of an image obtained with apparatus 600 is shown in FIG. 9. Platelets are shown as white dots, in comparison with **red blood cells which are of a darker shade**. [column 24, first paragraph]

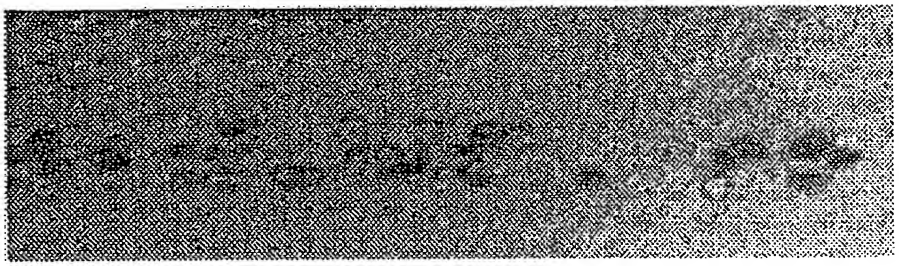

FIG. 9

All of the independent claims, as currently pending, recite methods and apparatus for measuring a flow characteristic within an optically accessible blood vessel and utilizing the measured characteristic for determining **a property of an inner wall of the blood vessel** (e.g., roughness and/or a roughness index).

As quoted above, the Summary of the Groner patent states "The present invention is directed to a method and apparatus **for analysis of blood** by use of reflected spectral imaging analysis." The Detailed Description describes a number of analyses of blood which could be performed, for example, measuring quantitative blood concentration measurements, measuring blood cell counts, measuring blood cell indices, and determining plasma constituents, determining blood flow characteristics of blood cells. None of the embodiments disclosed in the Groner patent disclose apparatus or method for using the imaging of the blood **vessel to determine a property of the wall of the blood vessel, nor is there any suggestion of same.** It is therefore the Applicant's belief that the claims as pending are patentable over the Groner patent.

The Examiner's attention is drawn to US Patent 6,104,939 to Groner. The embodiments disclosed within the '939 Groner patent are generally similar to those disclosed within the '120 Groner patent, insofar as the patentability of the claims as pending is concerned. As such, the arguments that were made regarding the patentability of the claims over the '120 Groner patent are equally applicable to the patentability of the claims over the '939 Groner patent.

It is noted that Fig. 2 of both the '120 and the '939 Groner patents contains a step of a flowchart of "Analyzing the analysis image for a characteristic of the subject's

vascular system." As there is no description in either of the patents of analyzing the analysis image to determine a property of a blood vessel wall, the Applicant asserts that this step of the flowchart should be interpreted as meaning analyzing the analysis image for a characteristic of blood of the subject's vascular system, as described above.

The Applicant now turns to a consideration of the combination of the Groner patents and the Flower patent. As described above, the Groner patents disclose forming a corrected reflected image by use of a velocity correction that allows moving cells to be extracted from a stationary background. The Applicant submits that it would not have been obvious to use this method of imaging moving cells to determine properties of a blood vessel wall as taught in any prior art reference known to the Applicant, in order to carry out the invention recited in the currently amended independent claims. Traditionally, properties of walls of a blood vessel would be determined by imaging the blood vessel, for example using angiographic imaging, as is the case in the Flower patent. According to the method of the Flower patent, a dye is injected into a blood vessel and the blood vessel is then imaged angiographically and lesions are diagnosed using the image. Workers of ordinary creativity in the field of blood vessel imaging were accustomed to imaging whole blood vessels, and would have seen no reason to consider adapting the techniques described in the Groner patent to their work. Furthermore, according to the Flower patent, a continuous flow of blood is analyzed, whereas the current patent describes and claims the analysis of the motion of discrete particles within the blood. Analysis of the blood flow at the scale of discrete particles provides analytical tools, which would not have been available or obvious to workers of ordinary creativity who were accustomed to analyzing images of blood as a continuum. For example, paragraph [0023] of the current application describes the following analysis, which can be performed on images of individual particles within the blood, but which is not performable using techniques described in the Flower patent:

> [0023] With perhaps the exception of the large, high-pressure vessels such as the aorta, if the limiting blood vessel walls are smooth, as in a healthy organism, blood generally flows in a laminar regime, thus creating regular, elongated patterns of moving erythrocytes, marking the flux-tubes. If however, the inner surfaces of the blood vessel walls are

rough, due for instance to the presence of arteriosclerotic plaques, the flux lines become irregular close to the blood vessel walls, since they follow the rough contour of the walls. **Particularly pronounced isolated protrusions from the blood vessel wall's inner surface, or partial occlusions may even give rise to turbulence, showing up in patterns of erythrocyte motion which clearly differ from those characterizing laminar flow.** Use can then be made of the line density of those irregularities as well as the amount of deviation of the flux lines near the vessel wall from straight lines, preferably by an average curvature parameter or by the distribution of the flux lines' curvatures, to quantify the roughness of the blood vessel walls. Such a measure can be performed even if the flow characteristics are known only partially, such as only in the proximity of the walls, which may be the case for imaging performed through the walls.

In light of the above discussion, the Applicant respectfully submits that there is no indication in the record that it would have been obvious for workers of ordinary creativity in the field of blood vessel imaging to try combining the Groner patent with the Flower patent, in the course of normal product development. By contrast, the present application as currently amended claims determining properties of a blood vessel wall by analyzing the flow of individual erythrocytes within the blood vessel. As described in the specification (and quoted above), the claimed invention *inter alia*, by use of the techniques described in the specification, utilizes (a) imaging moving erythrocytes within a subject's blood vessel, in order to (b) determine a property of a wall of the blood vessel. This combination is not taught or obvious in light of any prior art references known to the Applicant.

The Applicant believes the amendments and remarks presented hereinabove to be fully responsive to all of the grounds of rejection and objection raised by the Examiner. In view of these amendments and remarks, the Applicant respectfully submits that all of the claims in the present application are now in order for allowance. Notice to this effect is respectfully requested.

Respectfully submitted,

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